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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,262	ELLMAN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36 and 39-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14-28,32-36 and 39-50* is/are rejected.

7)☒ Claim(s) *11-13 and 29-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S-08

DETAILED ACTION

1. This action is in response to amendments filed on 6/6/05. Applicant has amended claims 1, 5, 13, 15, 19. Applicant has canceled claims 37 and 38. Claims 1-35 are method of using claims without therapeutic implications. Claims 36 and 39-50 are method of using for therapy claims. This is the second action on the merits. The application concerns using some peptide-mimic, enzyme inhibiting compounds for Alzheimer's disease treatment.

Response to Amendment

2. Applicants' amendment to the first line of the specification overcomes the objection concerning priority made in point #2 of the previous office action. Applicants' amendment to the specification concerning the description of the drawings and the new abstract overcome the objections made in point #3 and #4. Applicants' correction of the claim dependency overcomes the objection made in point #5. The deletion of "general" from the claims overcomes the indefiniteness rejection made in point #6. Applicants' addition of the structures of "CEL-S" *etc.* to the claims overcomes the indefiniteness rejection made in point #8.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 14-28, 32-36, and 39-49 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants repeatedly claim "substituted alkyl", "substituted aryl", and "substituted heteroaryl". These terms are defined in the specification in lines 9-15, page 11, lines 25-32, page 11, and lines 13-22, page 13 respectively. The definitions use open language "such as". Are there any limitations as to which substituents are claimed? How is the public to understand the metes and bounds of the claims? What exactly are the structures of the compounds, whose use Applicants claim? The Examiner suggests adding to the claims the specific substituents that may be attached to alkyl, aryl, or heteroaryl. Alternatively, Applicants can amend the specification to remove the open terms from the passages cited.

Applicants make four arguments concerning this rejection. They argue the rejected terms "are clearly defined in the specification on page 11, lines 9-15 and lines 25-32, and page 13, lines 13-22", that several examples exist of substituted alkyl groups *etc.*, that routine experimentation will be required to make the rejected compounds, and "substituted alkyl" *etc.* are terms recognized by the skilled organic chemist. These four arguments are not persuasive.

Firstly, the lines to which Applicants now point are the exact same lines used by the Examiner in the previous action to demonstrate that they use open language. Secondly, surely Applicants are not arguing that the terms "substituted alkyl" *etc.* are limited to mean only those working examples of such groups? The claims measure the invention. The U.S. Court of Customs and Patent Appeals wrote *In re Priest*, 199 USPQ 11 "We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim." *In re Prater*, 56 CCPA 1381, 1396, 415 F.2d 1393, 1405, 162 USPQ 541, 551 (1969)."

Thirdly, the rejection does not concern enablement for making the compounds, so the quality of experimentation is not at issue. Fourthly, substituted means that a hydrogen atom has been removed from an alkyl *etc.* radical and the free valence, thereby created linked to something else. The word "substituted makes clear the first step of that process but not the second since we do not know, and Applicants will not tell use what other group is to be attached to the "substituted alkyl" group. In the previous office action, the Examiner asked some specific questions regarding the structure of this newly introduced group. If Applicant cannot answer the questions, then how is the public to understand the scope of Applicants' claims?

In *Ex parte DIAMOND*, 123 USPQ 167, the Board of Patent Appeals and Interferences citing previous court decisions wrote, "[w]e also direct appellant's attention to *Ex parte Ritter et al.*, Patent File 2,631,152, wherein we affirmed a rejection of claims specifying "a substituted guanyl urea" as too broad and indefinite. The question there presented was similar to that involved in the rejection of claim 1 in the instant application. In the Ritter et al. case, we stated-

> "The term 'substituted' without modification or restriction includes all compounds wherein one or more of the atoms or radicals of the original compound have been replaced by one or more other atoms or radicals. Without any limitation on the character or number of substituents it becomes apparent that the quoted term may be considered inclusive of almost any possible substance and the claims under consideration are either of unlimited or indeterminate scope. We are of the opinion that the reasoning of the courts in *Schering Corp. v. Gilbert*, 68 USPQ 84, and *Hercules Powder Co. v. Rohm & Haas*, 70 USPQ 297, is controlling."

We are satisfied that there is no error in the examiner's rejection of claim 1."

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36 and 39-50 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any "neurodegenerative disorder". The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when

applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The four main issues are the lack of any correlation between clinical efficacy for "neurodegenerative disorder" treatment and Applicants' *in vitro* assay, the state of the prior art, evidence that a single nucleotide mutation in the cathepsin D gene results in production of an enzymatically inactive but stable enzyme leading the induction of a specific "neurodegenerative disorder", and the breadth of the claims.

There is an *in vitro* assay, drawn to inhibition of the aspartyl protease cathepsin D, described in lines 18-20, page 42 and in lines 1-35, page 44 with data on 18 compounds in Tables IV-VI. Applicants state in lines 29-35, page 62 that their inhibitors have "therapeutic value" and "would slow the production of a primary component of [Alzheimer's disease] AD". However, since no clinical results are reported and it is not recognized in the Alzheimer's disease therapeutic

arts this assay is correlated to clinical efficacy for the treatment of any "neurodegenerative disorder", this is speculation on Applicants part.

The state of the clinical arts in cathepsin D and "neurodegenerative disorder" treatment is provided by Ntais (Am J Epidemiol). Ntais (Am J Epidemiol) states in his conclusion in the paragraph spanning pages 533-534 there is little correlation between cathepsin D function and the risk for development of AD. *Kim (*Expert Opinion on Therapeutic Patents) states on page 429, in the second paragraph, that "specific cathepsin D inhibition may be useful for the treatment of breast cancer, malaria, and HIV-1 infection". Thus AD treatment is not an art-recognized use of Applicants' cathepsin D inhibitors.

Tyynelä (The EMBO Journal) reports in the first complete paragraph, second column, page 2786, the "neurodegenerative disorder" congenital ovine neuronal ceroid lipofuscinose (CONCL) in sheep, is caused by a deficiency in the lysosomal aspartyl proteinase cathepsin D. Thus, Applicants' inhibitors of cathepsin D may well induce the neurodegenerative disorder CONCL. Furthermore, in the first complete paragraph in page 2791, he states, "[i]n light of the results presented here, it will be important to ensure that therapeutic approaches directed at such amyloidogenic aspartyl proteinases do not affect neuronal

cathepsin D activity". Thus, Applicants' cathepsin D inhibitors could well worsen, and not treat, AD.

The scope of the claims involves all of the thousands of compounds of claim 36 as well as the hundred of diseases embraced by the term "neurodegenerative disorders". The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; Gerstmann-Straussler-Scheinker Disease (GSS); Pick's Disease; Diffuse Lewy Body Disease; Hallervordon-Spatz disease; progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration; progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmotic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); retinitis pigmentosa; Leber's Disease; and Hypertrophic interstitial polyneuropathy. These

exhibit a very broad range of effects and origins. For example, some give progressive dementia without other prominent neurological signs, such as Alzheimer's disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some are abnormalities of posture, movement, or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's disease and FTDP-17, and other such as Parkinson's clearly do not. Some affect only vision such as retinitis pigmentosa. Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's disease and Pick's disease both give progressive dementia without other prominent neurological signs. However, the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's disease. There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are different. Thus, FTDP-17 comes from

chromosome 17, Huntington's disease from 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to 21.

The great majority of these have no treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. The great diversity of diseases falling within the "neurodegenerative disorder" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's disease has produced are means of providing acetylcholinesterase inhibition, unrelated to the mechanism of action in this case.. Thus, the scope of claims is extremely broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants rely upon the limitation in the claims "wherein: said neurodegenerative disorder is characterized by the accumulation of amyloid plaques or by the accumulation of the accumulation of τ-fragments" as providing enablement for the claims. Frankly this hardly addresses the issues raised by the Examiner above, particularly the possibility that Applicants claimed method would exacerbate not benefit one of the diseases Applicants specifically indicate they wish to treat. According to MPEP §2106.02, " it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton*, 500 F.2d at 572, 183 USPQ at 37; *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979)."

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18 and 35 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-34 of U.S. Patent No. 6,150,416. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 13-34 are drawn to the inhibition generally of cathepsin D with the compounds of the present claims.

Applicants request to have this held in abeyance is noted.

Allowable Subject Matter

6. Claims 11-13 and 29-31 remain objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 1-10, 14-17, 19-28, and 32-34 still would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

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